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COMPARISON OF THE SYSTEMIC AND MICROVASCULAR RESPONSES TO UNCONTROLLED HEMORRHAGE IN ANESTHETIZED RABBITS

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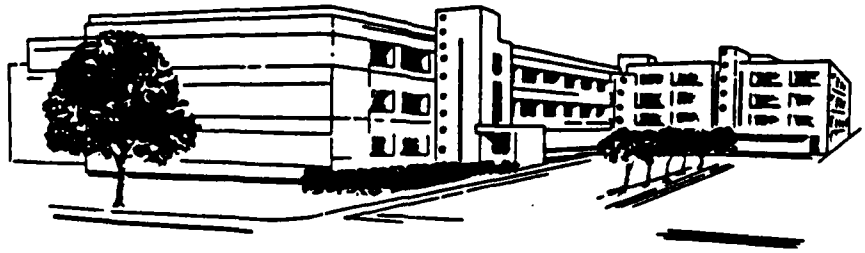

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Comparision of the Systemic and Microvascular Responses to Uncontrolled Hemorrhage in Anesthetized Rabbits, S.P. Bruttig et al

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COMPARISON OF THE SYSTEMIC AND MICROVASCULAR RESPONSES TO UNCONTROLLED HEMORRHAGE IN ANESTHETIZED RABBITS.

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ABSTRACT

We studied the systemic and microvascular responses to moderate, uncontrolled aortic or vena caval hemorrhage in skeletal muscle. Both systemic arterial pressure and systemic hematocrit fell following hemorrhage. Arterial pressure recovered moderately by 30 minute post-hemorrhage. The drop in hematocrit following hemorrhage was due to translocation of interstitial and intracellular water into the vascular compartment; ie., transcapillary refill. This change in hematocrit was similar following both types of hemorrhage. Transverse (pre-terminal) and terminal arterioles in the tenuissimus (skeletal) muscle of the rabbit constricted somewhat, however, the greatest constriction was in the terminal arterioles. Calculations of conductance and simulations of blood flow resulting from the aforementioned changes in diameter, pressure and hematocrit, suggest that immediately following hemorrhage, a re-distribution of muscle blood flow, to adjacent connective tissue, takes place. This re-distribution of blood flow abated 10 minutes after aortotomy, but continued more than 30 minutes following venotomy. It appears that the microvascular response to venous hemorrhage is similar to but fundamentally different than that to arterial hemorrhage.

INTRODUCTION

Knowledge of the microvascular response to hemorrhage is essential to understanding the total response to hemorrhage, and to developing or refining appropriate and effective resuscitative or treatment measures. To this end, many studies have been directed toward understanding the response to a controlled set of hemorrhage conditions (1-7). Controlled hemorrhage studies have been conducted either by bleeding from an intravascular catheter to a known pressure, and then maintaining that pressure for a period of time (8), or by removing a known volume of blood and studying the spontaneous recovery from that hemorrhage (9-11). The hallmark of controlled hemorrhage studies is the reproducibility they offer, and these studies have shown that a variety of responses are initiated throughout the body to protect the heart, lungs and brain, even at the expense of other, so-called non-vital tissues.

In contrast to studies of controlled hemorrhage in the laboratory, traumatic injury results in uncontrolled hemorrhage, often from major truncal blood vessels, where bleeding is difficult to arrest without surgical intervention. Hemorrhages of this type are often fatal (12), and given the varied nature of the injuries, this type of hemorrhage is difficult to reproduce experimentally. Consequently, there are few studies which have been directed at understanding the response to uncontrolled bleeding (13-16). These studies have often been conducted using peripheral blood vessels as the site of hemorrhage (14,15,17), or in the rare instance where a central vascular hemorrhage has been investigated, the emphasis of the study is on the systemic cardiovascular response (13,15). While traumatic injury many times involves injury to peripheral vascular tissues, uncomplicated, uncontrolled bleeding from peripheral blood vessels is rarely fatal (13). In addition, physiologic responses to injuries of peripheral vessels often include vasospasm, which aids in arresting hemorrhage. Finally, while there have been several

studies of the microvascular response to hemorrhage (1,4,6,7,18-21), none of these studies has addressed the microvascular responses to uncontrolled hemorrhage. Therefore, in an effort to understand the physiologic response(s) to potentially life-threatening hemorrhage, we have directed our attention to the systemic and microvascular responses following uncontrolled hemorrhage from major truncal vascular injuries.

Our previous studies into uncontrolled hemorrhage have been directed entirely at understanding the systemic vascular response to substantial hemorrhage. In these experiments, arterial pressures fell for a time to remarkably low levels (25-30 mmHg), and immediately following uncontrolled aortic hemorrhage total peripheral vascular resistance fell, rather than rose, and continued to fall for an additional 15 minutes (13,22-24). Furthermore, the substantial drop in hematocrit following this hemorrhage indicated a massive re-distribution of body fluid volume to the vascular compartment (22). Since the largest soft tissue mass in which to effect these peripheral changes is skeletal muscle, we felt that a better understanding of the microvascular perfusion of skeletal muscle during such circumstances was needed.

The present study focuses on the microvascular response of resting skeletal muscle to uncontrolled hemorrhage from a major truncal blood vessel; either the aorta or the vena cava. As such, this study represents the primary description of the arteriolar responses before, during and for 30 minutes following an uncontrolled hemorrhage from one of these truncal vascular sites. In addition, this study describes notable differences in the microvascular response to uncontrolled hemorrhage from a tear in either the abdominal aorta or the abdominal inferior vena cava.

MATERIALS AND METHODS

Animal Model. We chose to study the microvascular responses to uncontrolled hemorrhage in an established animal model; i.e., the tenuissimus muscle (7) of the rabbit (1.0 +/- 0.1 kg). This model has been well characterized (7,25-28) and has been used in the study of a variety of microvascular phenomena. In a modification

of previous descriptions, our model used the Hypnorm-sedated and urethane-anesthetized rabbit (25,27).

Aortotomy/Venotomy Preparation. After tracheostomy (PE 240 tubing), and catheterization of the carotid artery and the femoral artery and vein (PE 50 tubing), the hemorrhage site was prepared. The left flank was incised along the ventral border of the ileopsoas muscle. This allows entry into an essentially retroperitoneal space. The adjacent peritoneal wall, as well as the abdominal contents, were retracted ventrally, to expose either the aorta or the vena cava. The site for aortotomy or venotomy was exposed by blunt dissection, and the vessel of interest was momentarily clamped with a small "bulldog" type vascular clamp. A 5-0 or 6-0 braided cardiovascular suture (Tevdek; Deknatel, Queens Village, New York), swaged on a T-1 taper needle and previously moistened with glycerol, was put through and through the vascular wall in a single "stitch", but not tied. The needle was introduced at approximately a 45 degree angle (running caudad to cephalad) in either the lateral surface of the aorta or the medial surface of the vena cava. The aortic stitch was approximately 1/5 to 1/4 of the aortic diameter, and the stitch in the vena cava was approximately twice as large. The suture was drawn through to equalize the length of the free ends, and these were allowed to extend out of the operative site. The "bulldog" clamp was removed, and any bleeding from the suture holes was arrested by momentary pressure with a cotton swab.

Skeletal Muscle Preparation. The skin of the left hindlimb was surgically reflected to reveal the thin tenuissimus muscle, which runs longitudinally along the lateral surface of the thigh. Overlying connective tissue was carefully removed by dissection, and the central portion of the muscle was disconnected from its underlying connective tissue attachments as well. Great care was taken to avoid interrupting the vascular supply or drainage of the tenuissimus (shown schematically in Fig. 1, top panel), and to avoid any physical injury to the muscle. The muscle and its surrounding tissue were kept moist throughout the experiment by constant, low volume dripping of lactated Ringer's solution. The animal was then transferred to a plexiglass housing on the microscope stage. The free ends of the

cardiovascular suture were drawn through a PE 240 tubing (used as a guide for the exteriorization of the sutures), and the abdominal operative site was closed (sealed with a surgical adhesive; Histoacryl, B. Braun, Meisungen AG, Meisungen, W. Germany). The incision revealing the tenuissimus muscle remained open during the experiment.

Following this initial preparation, a light conducting prism was atraumatically introduced under the muscle for transillumination (6,25,27-31). The Köhler principle of illumination was applied to the light condenser, allowing for high resolution observation of the skeletal muscle microcirculation. After location of a suitable field for study using a 25X objective, the muscle was covered with a clear hyaluronic acid gel (Healon, Pharmacia AB, Uppsala, Sweden; 7,26) and a piece of oxygen-impermeable mylar film, in an effort to stabilize the extravascular environment. Then the muscle was brought into the plane of focus of a 50X microscope objective. The plexiglass housing was sealed, and the entire animal (from the neck down) was bathed in a gently flowing nitrogen environment (7,26,28).

Microvascular responses were continuously observed with the aid of an intravital microscope connected to both a video camera system and a videotape recorder (7,25,26,28,31). All measurements of vascular diameter were made off line, during a later analysis of the videotapes. Arterial blood gases were measured during the control period, 30 minutes after hemorrhage and 30 minutes into the resuscitation period. Systemic hematocrit (carotid artery) was measured from samples taken during the control period and at 5, 15 and 30 minutes after hemorrhage. Arterial pressure (femoral artery) was measured continuously, and heart rate was determined from the pressure tracing.

The microvascular field (an example of which is shown in Fig. 1 bottom panel) was observed prior to the beginning of the experiment. In addition, arterial blood gases and hematocrit were measured, arterial pressure was monitored, and heart rate was determined from the arterial pressure tracing. Animals were included in this study only if they met established inclusion criteria. These included:

1) Mean arterial pressure during the control period >60 mmHg
2) pO_2 >70 mmHg during the control period
3) Heart rate in the control period > 240 beats per minute
4) Terminal and transverse arterioles constrict in room air, and terminal arterioles are 3-6 μ in diameter during the control period when bathed in nitrogen. Terminal arterioles which were completely closed for long periods during the control period were excluded from the study
5) Brisk flow in the transverse arteriole during the control period
6) Brisk flow in the terminal arteriole, when open, during the control period
7) No damage or bleeding in the tissue when viewed through the microscope
8) Significant drop in systemic mean arterial pressure following hemorrhage
9) Significant drop in systemic hematocrit following hemorrhage

NOTE: While the acceptable value for mean arterial pressure seems low compared to normal adult values, a mean arterial pressure of 60-80 mmHg is normal for anesthetized rabbits of this size. In fact, when we had the opportunity to measure arterial pressure in conscious rabbits (1.0 +/- 0.1 kg), the values were within the same range as those values reported for control conditions in this study.

Experimental Protocol. The experiment was divided into three phases: control period (10 minutes); hemorrhage (3-4 minutes); spontaneous recovery period (27 minutes); and a resuscitative period (30-90 minutes) which will be reported in subsequent communications.

Calculations. Initial blood volume was estimated as 80 ml per kilogram. The hemorrhage volume was assumed to be 30% (by comparing the decreases in mean arterial pressure and hematocrit following uncontrolled bleeding in the rabbit with those observed in rabbits following 30% fixed-volume hemorrhage in 3 minutes (7) or with observed responses of pigs following aortotomy with a measured hemorrhage volume of 33% (13)). While diameter measurements were made by direct observation of off-line videotape images, these diameter measurements have been presented as standardized values (i.e., each diameter measurement for any one animal was standardized to the measurement during the control period). The data for arteriolar diameter were entered into a model which accounts for changes in apparent viscosity of blood at extremely small arteriolar diameters (7). Arteriolar diameters were also used to calculate arteriolar conductances as estimates of blood flow. These calculations of conductance account not only for the law of Poiseuille but also for the dependence of apparent viscosity on luminal vessel diameter (7). Finally, these estimates of conductance were used to calculate TE/TR ratios as an additional indication of blood flow distribution.

RESULTS

Control Conditions. Prior to hemorrhage, systemic physiologic values (pO_2, pH, pCO_2, HCO_3^-, Base Excess) were all within the normal range (Table 1).

TABLE 1
SYSTEMIC ARTERIAL PHYSIOLOGIC VALUES PRIOR TO HEMORRHAGE

	Aortotomy		Venotomy	P-val
pO_2	81.29+/-4.77 (7)*	mmHg	80.67+/-5.37 (6)	NS
pH	7.33+/-0.02 (7)		7.34+/-0.03 (6)	NS
pCO_2	47.17+/-1.22 (7)	mmHg	49.05+/-2.50 (6)	NS
HCO_3-	25.30+/-1.18 (7)	meq/l	26.83+/-1.68 (6)	NS
B.E.**	0.44+/-1.30 (7)		2.05+/-1.84 (6)	NS

* Numbers in parentheses represent the number of animals for each determination.
** Base Excess.

Blood Pressure (MAP). Predictably, uncontrolled hemorrhage, whether from an arterial or venous vascular site, resulted in a profound decrease in mean arterial pressure. Within 3 minutes following aortotomy (7 animals), MAP fell an average of 65%, but recovered somewhat in the ensuing 30 minutes to 50% of control (Fig. 2, top panel). Venotomy (6 animals) resulted in a 50% decrease in MAP in 3 minutes, however, there was essentially no spontaneous recovery (Fig. 2, top panel).

Hematocrit. Hemorrhage also resulted in hemodilution. After aortotomy, hematocrit fell 20% in 5 minutes. By 30 minutes post hemorrhage, hematocrit had fallen to 74% of control (Fig. 2, bottom panel). Similar results were observed following venotomy, with a 19% drop in 5 minutes and an hematocrit at 30 minutes that was 75% of control values (Fig. 2, bottom panel).

Blood Gases and Acid Base Status. Either type of hemorrhage produced metabolic acidosis, characterized by decreases in arterial plasma pH, HCO_3^- and base excess (Fig. 3, left and right panels). Arterial pO_2 was unchanged by either type of hemorrhage, but pCO_2 decreased substantially following both types of hemorrhage (Fig. 3, left panel).

Terminal Arterioles. Terminal arterioles constricted 25% within 1 minute following aortotomy, and continued a gradual narrowing (to 65% of control) during the next 9 minutes (Fig. 4, top panel). Subsequently, these arterioles began a gradual dilation and returned to essentially control levels by 30 minutes after hemorrhage. When these data were standardized to control values (i.e., microvascular diameters for each animal at any time "t" divided by that same vessel's diameter during the control period), the pattern of response was similar to that observed for the raw data. Calculated and standardized conductances for these arterioles decreased dramatically (to 7% of control levels in less than 5 minutes; Fig. 4, bottom panel). By 30 minutes after hemorrhage, conductance had risen steadily to 93% of control levels.

Venotomy also resulted in terminal arteriolar constriction (to 36% of control by 5 minutes; Fig. 4, top panel). Although some dilation occurred subsequently, the overall pattern was one of constriction throughout the 30 minute post hemorrhage period. Calculated and standardized conductance decreased to very low (essentially zero) levels following venotomy (Fig. 4, bottom panel). The decreased conductance persisted throughout the entire spontaneous recovery period, except for a brief burst of flow 10 minutes after the venotomy.

Transverse Arterioles. Following aortotomy, the diameter of the transverse arterioles decreased 25% within the first 5 minutes (Fig. 5, top panel). Thereafter, there was a gradual vasodilation, actually exceeding control levels by 13% at 30 minutes post hemorrhage. Calculated and standardized conductance was decreased 60% in the first 15 minutes after aortotomy hemorrhage, returned to control levels by the eighteenth minute post-hemorrhage, and exceeded control values by 80% at the end of the recovery period (Fig. 5, bottom panel).

Following venotomy, transverse arterioles constricted nearly 20% (at 5 minutes post-hemorrhage) and remained somewhat constricted throughout the recovery period (Fig. 5, top panel). Calculated and standardized conductance of transverse arterioles decreased nearly 40% in the first two minutes, and to 50% by 5 minutes after venotomy hemorrhage (Fig. 5, bottom panel). Recovery of conductance was blunted following venotomy (to 73% of control at 16 minutes), and it remained considerably below control levels throughout the post-hemorrhage period.

Terminal/Transverse Arteriolar Conductance Ratio. If one assumes that the microvessels sampled in this study are representative of the vessels throughout the tenuissimus muscle, then the microvascular blood flow patterns described here should be reasonably descriptive of flow in the entire tenuissimus muscle and for skeletal muscle in general (32-35). It follows then that the ratio of conductances (terminal arteriole/transverse arteriole) should reveal the fractional distribution of blood flow between the muscle fibers, per se, and should also reveal that flow going through the muscle to the adjacent connective tissue. Since there was less change in transverse than in terminal arteriolar conductance, decreases in this ratio primarily reflect the substantial decreases in terminal arteriolar conductance. The calculations expressed in Figure 6 indicate that the muscle blood flow remaining after aortotomy hemorrhage was diverted to connective tissue for about 10 minutes; then an increasingly larger fraction of the total blood flow (to a maximum of 50%) returned to the skeletal muscle fibers by 20 minutes post-hemorrhage. The same figure (Fig. 6) indicates that following venotomy,

essentially all blood flow was diverted to the connective tissue, and most of the blood flow in the tenuissimus remained diverted to connective tissue throughout the spontaneous recovery period.

It should also be noted that approximately one third of the animals initially assigned to this study died as a result of the aortotomy or venotomy. We assume that these deaths were due to a larger than normal hemorrhage volume (from too large a tear in the aorta or vena cava). In the animals who died, pressure also fell quickly to near 20 mmHg and, after varying periods of time, continued to fall to values ranging between 10 and 15 mmHg. Terminal arterioles usually constricted completely, and within 1-2 minutes the transverse arteriole also constricted maximally. There may have been profound constriction in more proximal microvessels, as flow through the tenuissimus muscle ceased, even in transverse arterioles which had not constricted completely. The heart apparently shifted from normal sinus rhythm to a ventricular rhythm, owing to continued underperfusion of the cardiac bed. Within 4-5 minutes, pressure dropped off to near zero and the animal expired. Events such as these reinforce the unpredictable nature of studies of aortotomy and venotomy as difficult yet realistic models of uncontrolled hemorrhage.

DISCUSSION

Uncontrolled Aortic Hemorrhage. Uncontrolled arterial hemorrhage is a rarely studied cardiovascular phenomenon, probably owing to the difficulty in obtaining reproducible responses to this insult. The few studies which have been conducted have focused on systemic vascular responses to either peripheral vascular injuries (14,15,17) or to a truncal vascular lesion (13-15,22). Recent studies have also focused on survival, following attempted resuscitation of uncontrolled bleeding (14,15,17,23,24). In the only studies to report cardiodynamic responses to uncomplicated, uncontrolled aortic hemorrhage (13,23,24), systemic vascular resistance decreased significantly for a period of time

after the hemorrhage. The implication from that response (peripheral vasodilation) contradicts classically held views that the appropriate vascular response to substantial hemorrhage is peripheral vasoconstriction (36). Such results require verification by other, independent techniques; intravital microscopy being one of those techniques.

The present study of uncontrolled truncal arterial hemorrhage provides a unique view of the local microvascular response to massive blood loss following a singular traumatic injury (i.e., aortotomy). This study indicates that the skeletal muscle microvascular responses to uncontrolled hemorrhage include a short-lived but global flow reduction apparently effected by a differential arteriolar constriction. These constrictor changes effect both a rise in peripheral vascular resistance (which raises systemic arterial pressure somewhat) and a re-distribution of blood flow from muscle fibers to adjacent connective tissue elements. The time course of this flow re-distribution was coincident with the period of greatest post-hemorrhage hemodilution and implicates the connective tissue adjacent to skeletal muscle as a likely site for a major portion of this fluid translocation. Interestingly, this response is similar to that observed for controlled arterial hemorrhage in the same preparation (7).

Observations from the present study would not support the notion of peripheral vasodilation in response to aortotomy. However, pigs and rabbits may respond differently to uncontrolled hemorrhage, therefore unqualified extrapolation of data from the present study to previous studies involving pigs may be unwarranted.

Uncontrolled Vena Caval Hemorrhage. To our knowledge, there are no systematic studies of the microvascular response to uncontrolled vena caval hemorrhage existing in the scientific literature. Therefore, the present study represents the pioneering effort in this area. Nevertheless, this study demonstrates that, like aortotomy hemorrhage, the microvascular responses to vena caval hemorrhage include a global reduction of blood flow, effected by prolonged vasoconstriction and a sustained (at least for the course

of these experiments) diversion of blood flow from the muscle fibers to the surrounding connective tissue. Interestingly, the prolonged microvascular constriction within the tenuissimus, presumably a reflection of a similar response throughout the skeletal muscle beds, had little effect on systemic arterial pressure. Like other forms of hemorrhage (9,13), this venotomy caused the rapid translocation of interstitial and intracellular fluid to the vascular space, i.e., transcapillary refill. While the time course for the hemodilution was similar to that for either controlled or uncontrolled arterial hemorrhages, i.e., 15-20 minutes (present study and 7), the blood flow reduction to skeletal muscle fibers, per se, continued throughout the spontaneous recovery period.

Similarities and Differences Between Aortic and Vena Caval Hemorrhage. Both types of hemorrhage resulted in a rapid loss of intravascular volume and a consequent rapid decrease in mean arterial pressure. The drop in intravascular hydrostatic pressure, rearrangements in pre- to post-capillary resistance (37), and the subsequent imbalance in Starling forces which likely occurred at the capillary, all favor fluid absorption from the interstitium.

In addition, the results of this study clearly demonstrate that in response to both types of uncontrolled hemorrhage, muscle blood flow is diverted from the skeletal muscle fibers per se to the surrounding connective tissue. The reasons for this shift in blood flow are only partially understood. It appears that β-adrenergic mechanisms may be responsible for this shift (2,3,27-29,31). Furthermore, it has been shown that the filtration coefficient (CFC) of capillaries in the connective tissue is significantly higher than that for capillaries in skeletal muscle tissue per se (38). It appears likely that this shift in blood flow is effected to allow or augment the rapid transcapillary refill.

This "transcapillary refill" aids in plasma volume repletion and should improve flow properties of the blood, but occurs at the expense of oxygen carrying capacity by diluting the remaining circulating red cell mass. Furthermore, this decrease in oxygen carrying capacity occurs at a time when cardiac output is at its nadir (13). These observations indicate that the

microvascular response to hemorrhage favors increases in rheologic factors (in an effort to maximize tissue perfusion) over oxygen-carrying capacity; at least within some physiologically tolerable range. In addition, the fact that this hemodilution occurs throughout the spontaneous recovery period indicates that the rabbit does not have a contractile spleen (a similarity shared with man), and therefore cannot autotransfuse stored red blood cells in response to hemorrhagic hypotension. Finally, massive fluid reabsorption also results in the dilution of plasma proteins, which effectively reduces plasma oncotic (protein osmotic) pressure. Moreover, fluid reabsorption reduces the blood buffering capacity by diluting plasma bicarbonate and other buffer molecules.

While both types of hemorrhage are eventually characterized by a decrease in venous return, we speculate that the sensation of volume loss from the central venous compartment (by cardiopulmonary receptors) is perceived more rapidly than an equivalent volume loss from the arterial compartment. In addition, it is likely that the cardiovascular system can differentiate between a reduction of myocardial afterload (diastolic pressure) and a reduction in myocardial pre-load (venous return, indicated by central venous pressure). However the difference in the type of hemorrhage is perceived, it is obvious that the microvascular responses to the two types of hemorrhage are distinctly different (i.e., transient vs. prolonged terminal arteriolar constriction, prolonged re-distribution of blood flow to adjacent connective tissue, moderate vs. negligible recovery in systemic arterial pressure).

The systemic responses to substantial hemorrhage from major truncal vascular sites have many phenomena in common. In both types of hemorrhage, vascular volume is lost and arterial pressure falls rapidly. However, a venous hemorrhage equivalent in rate and magnitude to the aortic hemorrhage, requires a venous hemorrhage site approximately twice as large as its aortic counterpart. The reason appears to be the much-reduced perfusion pressure on the venous side. Hematocrit falls rapidly in both cases, and changes in arterial blood gases and acid base are similar. Of the variables observed in this study, the major differences between the two types of

hemorrhage appear to be the vasoconstrictor activity of the terminal arterioles, the subsequent re-distribution of blood flow, and the disparity in recovery of mean arterial pressure. With arterial hemorrhage, terminal arterioles constrict significantly, but escape this constrictor activity several minutes (15-20 minutes) after the onset of hemorrhage. With venous hemorrhage, vasoconstrictor activity persists throughout the post-hemorrhage spontaneous recovery period. Since systemic arterial pressure and hematocrit changes, as well as plasma volume recoveries were similar in both groups immediately following hemorrhage, the reason(s) for differences in arteriolar vasoconstrictor activity are unclear at present. Finally, the failure of systemic arterial pressure to recover following venotomy, in the face of prolonged peripheral vasoconstriction is still without explanation.

One can speculate that the most likely differences in the experimental models are the sites at which the bleeding took place and the length of time that the loss in pressure (stretch) took to reach various pressure and volume sensing sites for processing. In addition, it is also possible that the central neural processing of these two types of hemorrhage is different, and as a result, the efferent neural control of the microvasculature, in response to the two different types of hemorrhage, is substantially different. In any case, from the observations and calculations presented here, it is apparent that an uncontrolled central venous hemorrhage is interpreted by the body as a somewhat different and possibly a more devastating insult than its arterial counterpart.

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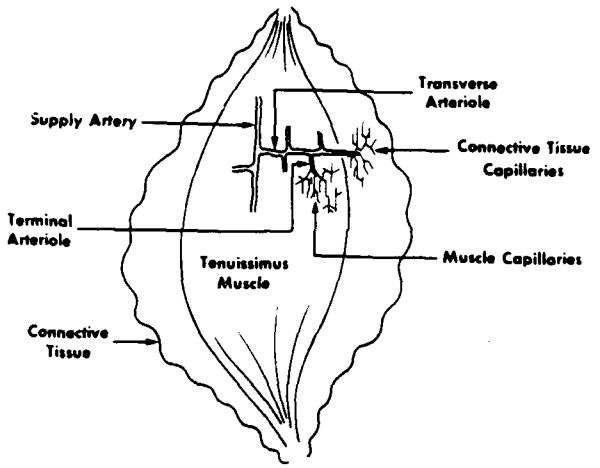

Figure 1. **Top Panel.** A schematic representation of the microvascular distribution within the tenuissimus muscle of the rabbit. Though the figure only shows one network of vessels, there are many of these networks throughout the muscle. **Bottom Panel.** Photomicrograph of a microvascular field within the tenuissimus muscle of the rabbit. The pre-terminal (transverse = TR) arteriole is shown with blood flowing from left to right. The terminal (TE) arteriole is seen branching off the TR in a nearly perpendicular fashion. There are three skeletal muscle fibers (oriented vertically) in this micrograph.

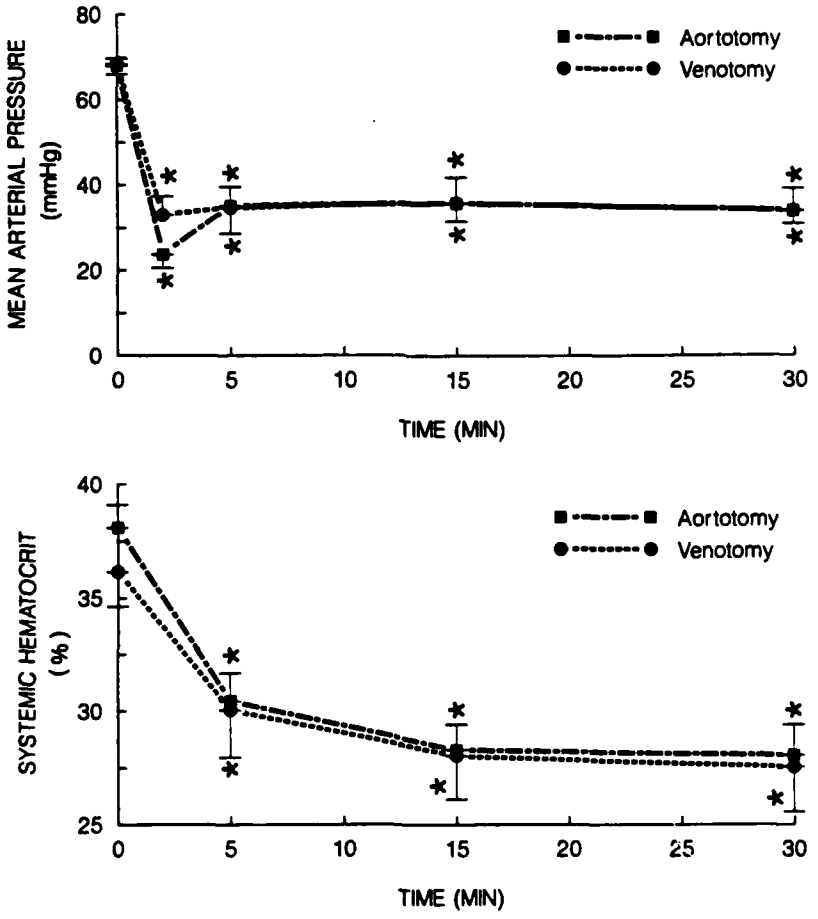

Figure 2. Perfusion pressure and hematocrit prior to and following two types of uncontrolled hemorrhage. Top Panel. The changes in mean arterial pressure (mean +/- SEM) are presented. Bottom Panel. The changes in systemic arterial hematocrit (mean +/- SEM) are presented.

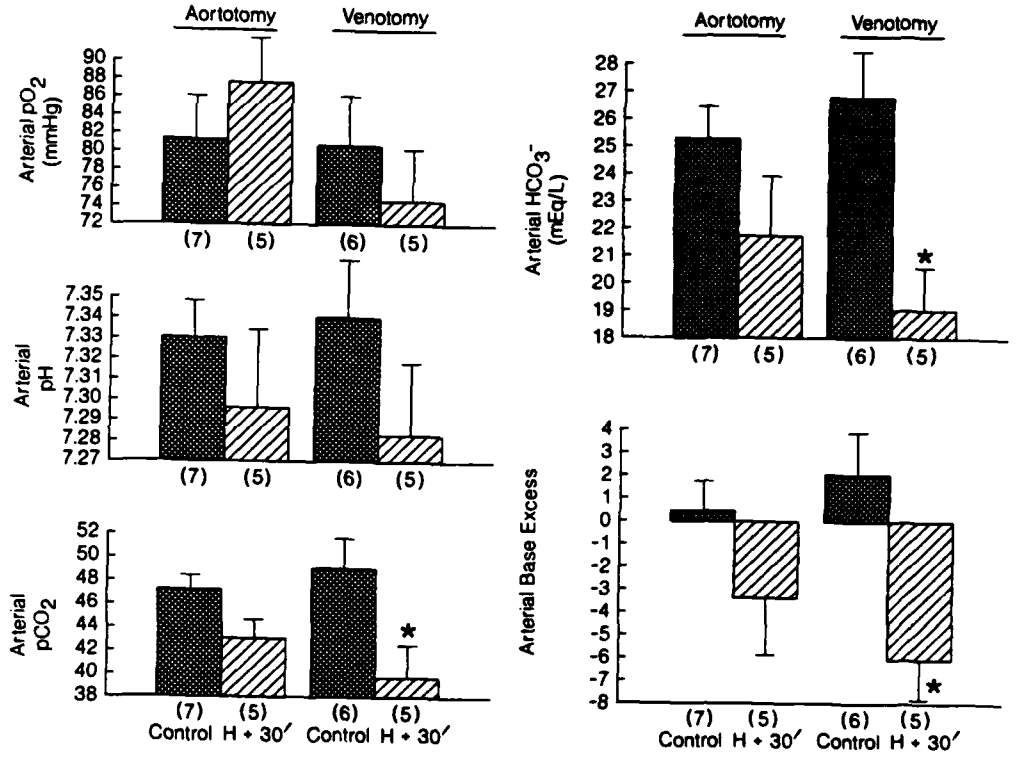

Figure 3. Blood gases and acid base status before and 30 minutes after uncontrolled hemorrhage. **Left Panel.** Changes in arterial pO2, pH and pCO2 (mean +/- SEM) are presented. **Right Panel.** Changes in arterial HCO3- and Base Excess (mean +/- SEM) are presented.

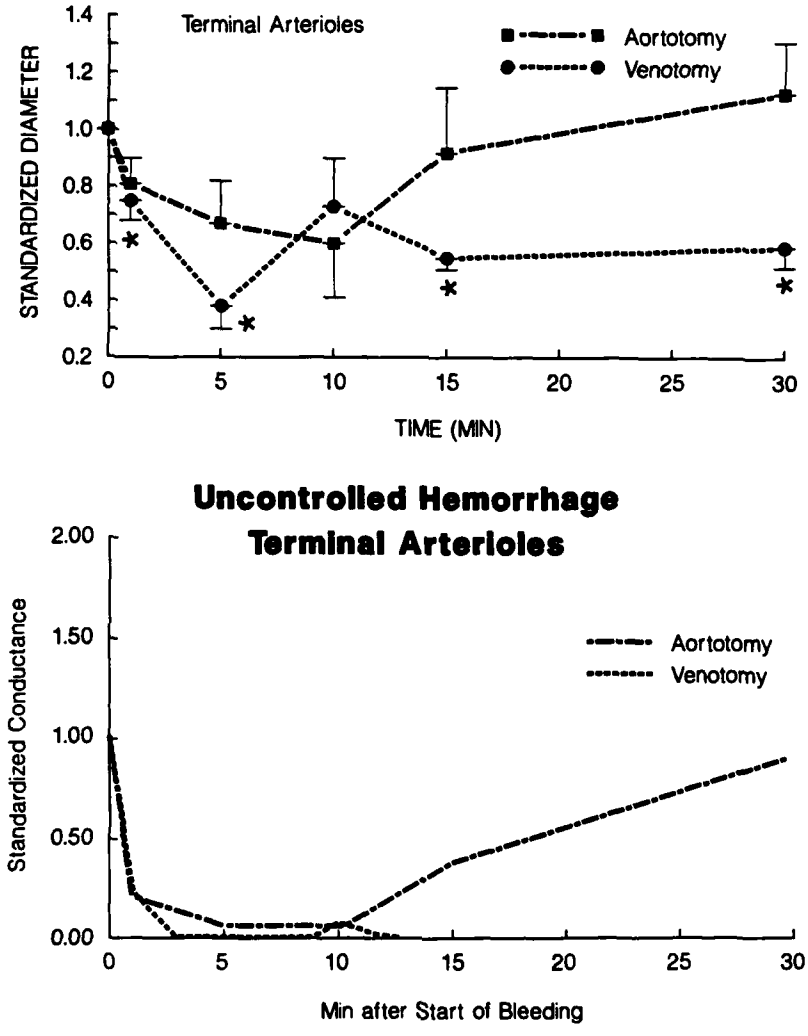

Figure 4. Standardized diameters and conductances for terminal arterioles before and following two types of uncontrolled hemorrhage. **Top Panel.** Arteriolar diameters, standardized to control values; means +/- SEMs are presented. **Bottom Panel.** Arteriolar conductances, as an indication of arteriolar blood flow, are presented. Conductances were calculated from mean data for arterial pressure, systemic hematocrit and arteriolar diameter.

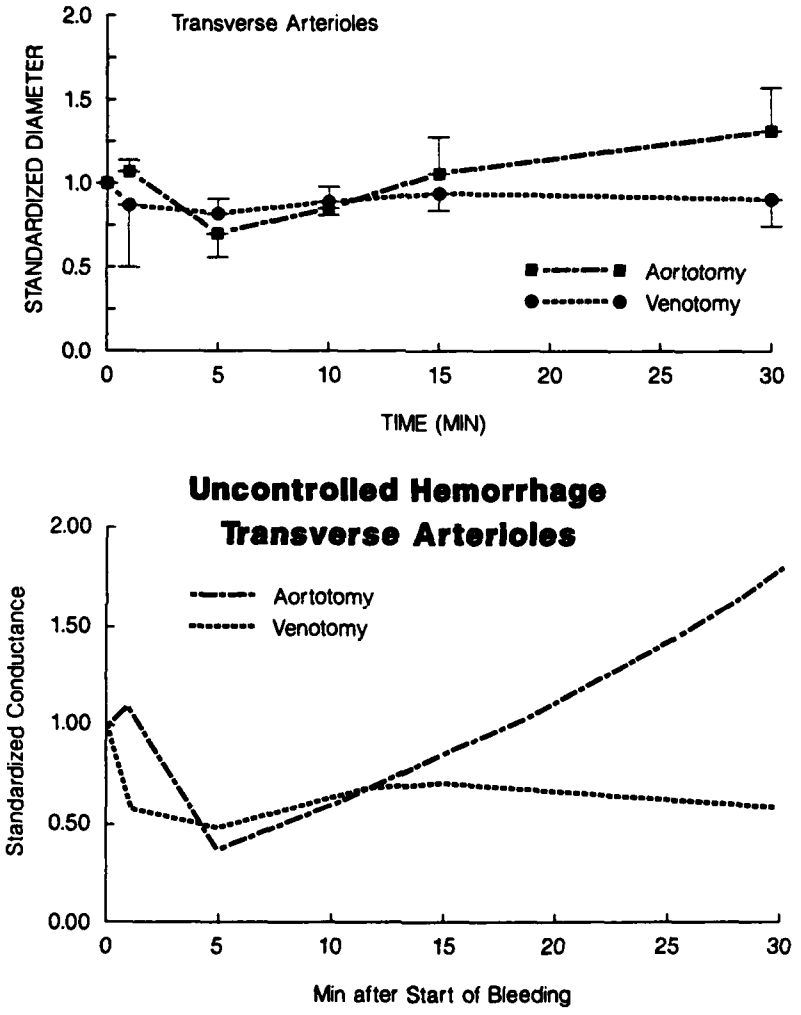

Figure 5. Standardized diameters and conductances for transverse arterioles before and following two types of uncontrolled hemorrhage. **Top Panel.** Arteriolar diameters, standardized to control values; means +/- SEMs are presented. **Bottom Panel.** Arteriolar conductances, as an indication of arteriolar blood flow, are presented. Conductances were calculated from mean data for arterial pressure, systemic hematocrit and arteriolar diameter.

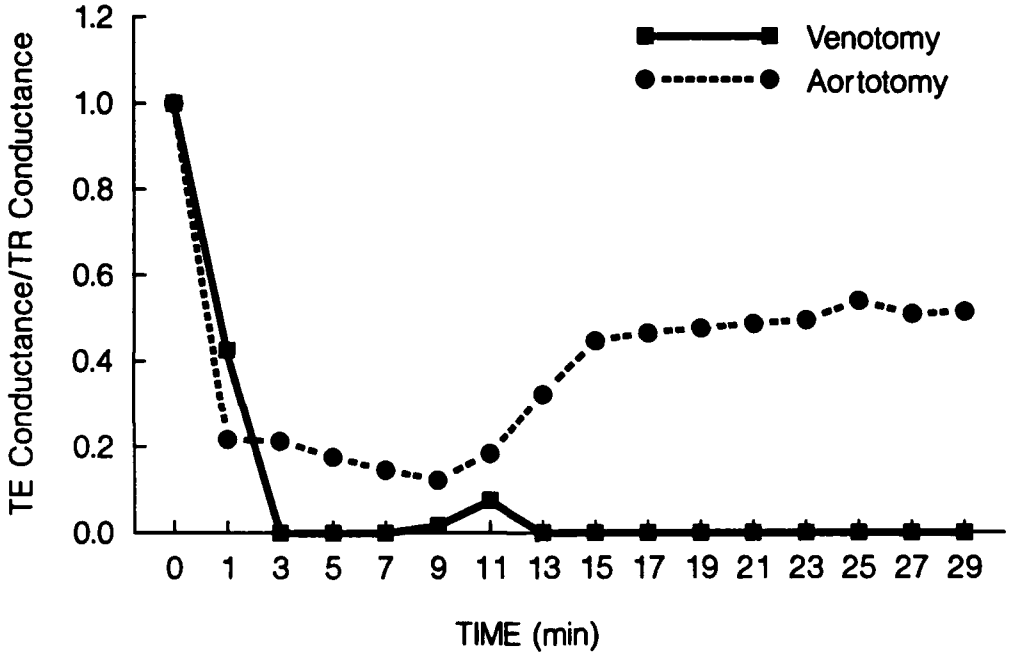

Figure 6. Terminal (TE)/Transverse (TR) arteriolar conductance ratios, as measures of the distribution of the remaining blood flow following two types of uncontrolled hemorrhage, are presented. The curves are derived from the data presented for arteriolar conductance in Figs. 4 and 5.

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